

### **REMARKS**

Applicants have addressed the informal objections to claims 59-87 with respect to correcting "A" to "The" in the dependent claims. A "the" has been added in claim 68." With respect to "octacalcium," applicants intended "octacalcium" and not "octocalcium." In fact, there is a book "Octacalcium Phosphate" by Lawrence Chow which can be located by a simple internet search.

Applicants' note that claims 65-72 were objected to based on format, but no prior art was cited against them. So these claims are now allowable.

New claim 88 is added to specifically cover a situation within the scope of the invention and within the scope of the disclosure wherein the solution is a "solution/dispersion," i.e., where at least some components of the solution are partially soluble. Support for this is, e.g., in paragraph 0012 of the published application 2007/0134285.

Applicants respectfully request reconsideration of the rejection of claims 58-64 and 73-87 as anticipated by Bohner et al. 6,733,582.

Applicants' independent claim 58 is specifically directed to a process for the production of a composite material comprising collagen, brushite and one or more glycosaminoglycans. The process comprises

providing an acidic aqueous solution comprising collagen,  
a calcium source and a phosphorous source and one or  
more glycosaminoglycans, and

***precipitating the collagen, the brushite and the one or  
more glycosaminoglycans together from the aqueous  
solution to form a triple co-precipitate.***

Accordingly, it is an express requirement of claim 58 that collagen, the brushite, and the glycosaminoglycan(s) are precipitated together from the aqueous solution ***to form a triple co-precipitate***. Bohner et al. fail to disclose or suggest this express requirement.

The Bohner et al. patent relates to brushite cements for surgical purposes. The cement comprises a basic calcium phosphate, an acidic calcium phosphate, water, and magnesium for setting the end product. Column 2, lines 15-49. As stated in column 4, lines 12-27, collagen granules can be set into the brushite matrix to control the resorption rate of the cement. The consistency of the cement can be controlled by using a biodegradable polymer, which can be *inter alia* hyaluronic acid (a glycosaminoglycan) or collagen. Column 5, lines 4-19. Although calcium phosphate, collagen, and hyaluronic acid are disclosed, these are not disclosed by Bohner et al. as in the form of a triple co-precipitate in the context of a precursor material or composite biomaterial.

While it is evident from Bohner et al.'s general description that their phosphate, collagen, and hyaluronic acid are not "precipitated together ... to form a triple co-precipitate," their working examples underscore that this neither contemplated, nor suggested, nor inherent:

#### Example 1

This example discloses a cement with a composition: 1.33 g  $\beta$ -TCP (mean particle diameter in volume: 1.1 micrometer), 0.67 g Mono Calcium Phosphate Monohydrate, 25 mg  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 1 g TCP granules (400 to 500 micrometers in diameter) and (x) mg  $\text{Na}_2\text{SO}_4$  or  $\text{MgSO}_4$ . The mixing liquid was 1 g of an aqueous hyaluronic acid solution. The samples were prepared as follows: (i) 30 s mixing of the powders with the solution, (ii) insertion of the paste into the tip of a cement syringe, (iii) measurement of the setting time, (iv) ejection of the sample out of the syringe, (v) aging in 2 mL d.i. water for 24 hours, (vi) drying. The end-product of the reaction was brushite. There is no disclosure or suggestion of triple co-precipitation.

#### Example 2

The cement composition was: 1.33 g  $\beta$ -TCP (mean particle diameter in volume: 1.1 micrometer), 0.67 g MCPM, 25 mg  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 1 g TCP granules (400 to 500 micrometers in diameter), 20 or 50 mg  $\text{Na}_2\text{O}_4$  or  $\text{MgSO}_4$ , and 0 or 150 mg  $\text{Ca}_2\text{P}_2\text{O}_7$ . The mixing liquid was 1 g of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). The samples were prepared and analyzed as explained in

the first example. Results show that the setting time of the cement was significantly increased by replacing sodium sulfate with magnesium sulfate, and significantly decreased when  $\text{Ca}_2\text{P}_2\text{O}_7$  was added to the cement paste. There is no disclosure or suggestion of co-precipitation.

#### Example 3

This describes in vivo experiments using cement with a composition: 5.33 g  $\beta$ -TCP (mean particle diameter in volume: 1.1 micrometer), 2.66 g MCPM, 100 mg  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 4 g TCP granules (400 to 500 micrometers in diameter), 100 mg  $\text{Na}_2\text{SO}_4$  or  $\text{MgSO}_4$ , 0 or 600 mg  $\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$ , and 0 or 600 mg  $\text{Ca}_2\text{P}_2\text{O}_7$ . The mixing liquid was 4 mL of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). There is no disclosure or suggestion of triple co-precipitation.

#### Example 4

This describes in vivo experiments using different cements:

Cement samples were prepared by mixing for 60 seconds with a spatula the cement powder with the mixing liquid. Afterwards, the paste was poured into a syringe and the paste was injected with the syringe into a cylindrical defect (8 mm diameter) made in the proximal or distal femora/humerus of a sheep. Three compositions and one control (empty hole) were tested pro sheep.

The first composition was a commercial product, Norian SRS, which contains as end-product a poorly-crystallized carbonato-apatite.

The second composition was: 0.96 g  $\beta$ -TCP (mean particle diameter in volume: 1.1 micrometer), 1.92 g MCPM, 80 mg  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 6.72 g TCP granules (125 to 1000 micrometers in diameter), 100 mg  $\text{Na}_2\text{SO}_4$ , 600 g  $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ , and 600 mg  $\text{Ca}_2\text{P}_2\text{O}_7$ . The mixing liquid was 4 mL of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s).

The third cement composition was: 5.33 g HA (mean particle diameter in volume: 0.08 micrometer), 2.66 g MCPM, 20 mg  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 4 g TCP granules (125 to 1000 micrometers in diameter), 100 mg  $\text{Na}_2\text{SO}_4$ , and 600 mg  $\text{Mg}_2\text{P}_2\text{O}_7$ . The mixing liquid was 6 mL of an aqueous xanthan solution (viscosity: 100 mPa·s).

As in the previous examples, there is no disclosure or suggestion of triple co-precipitation.

#### Example 5

Cement samples were prepared according to the following composition: 1.2 g HA (mean particle diameter in volume: 2 micrometer), 0.6 g MCPM, 1 g HA granules (200 to 300 micrometers in diameter), and 0 to 0.1 g gentamicin sulfate (powder). The mixing solution (1.2 mL) was a 0.1M aqueous  $\text{Na}_2\text{HPO}_4$  solution containing 0.5 weight-% xanthan gum. Again, here there is no disclosure or suggestion of triple co-precipitation.

Accordingly, the Bohner et al. disclosure fails to even suggest a process for triple co-precipitation. Although the specification does recite that hyaluronic acid can be used, it is never used in conjunction with collagen in any example. But even if collagen were to be used in conjunction with calcium, phosphate and hyaluronic acid, it is not co-precipitated. Rather it is added as granules, to control the resorption rate of the cement, leading to a conglomerate structure of the finally set cement, whereby the granules are embedded in the brushite matrix formed by the setting process. Alternatively, it is added as a biodegradable polymer for controlling the consistency of the cement paste.

In view of Bohner et al.'s failure to disclose or suggest this express requirement, applicants respectfully submit that claim 58 neither anticipated nor obvious.

Claims 59-64 and new claim 88 depend from claim 58 and are therefore respectfully submitted to be patentable for the same reasons as claim 58, and by virtue of the additional requirements therein.

The remaining claims 73-87 are respectfully submitted to be patentable because a required element thereof is a "triple co-precipitate of collagen, brushite and one or more glycosaminoglycans." The cited references do not disclose or suggest this express requirement, as explained above in connection with claim 58.

Moreover, this physical distinction is significant as explained in applicants' paragraphs 0007 and 0012:

It has been found that such a [simply mixed] material, although biocompatible, produces limited in-growth of natural bone when in the human or animal body and no remodeling of the calcium phosphate phase of the synthetic material.

The microstructure of a co-precipitate is substantially different from a material formed from the mechanical mixing of its components.

In view of Bohner et al.'s failure to disclose or suggest this express requirement, applicants respectfully submit that claims 73-87 are neither anticipated nor obvious.

**Conclusion**

In view of the foregoing, applicants request favorable reconsideration and allowance of all pending claims.

Respectfully submitted,

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